REMARKS

Applicants respectfully request reconsideration and allowance of all pending claims presented herein.

I. Status of the Claims

Applicants have amended claim 1 to more particularly define the subject matter claimed therein, and to incorporate the details of dependent claim 4 (now canceled). Support for the amendments may be found at, for example, paragraph [0011] and Example 1 of the published application (U.S. Publication No. 2005/0175536), as well as in now canceled claim 4.

In addition to the amendment of claim 1 and the cancelation of claim 4, Applicants have amended: claims 6, 7 and 16 (to correct claim dependencies), claims 8-10 (amended to depend from claim 1), and claims 11-14 and 17 (to clarify and/or correct grammatical issues therein).

Accordingly, claims 1, 2 and 5-18 are now pending in the application. Claims 6-15 stand withdrawn for being directed to a non-elected species and/or invention. However, Applicants respectfully point out that, in view of the claim amendments presented herein, all claims now depend directly or indirectly from claim 1. Accordingly, Applicants request that withdrawn claims 6-15 be rejoined and further examined, after claim 1 has been allowed.

In view of the foregoing, claims 1, 2, 5 and 16-18 are currently under examination.

II. Rejection under 35 U.S.C. §112, Second Paragraph

Claims 1, 2, 5 and 16-18 have been rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting an essential step, that being the active step of autoclaving. In response thereto, Applicants have amended claim 1 to affirmatively recite an autoclaving step. Applicants therefore request withdrawal of the present rejection.

III. Rejection under 35 U.S.C. §103(a)

Reconsideration is requested of the rejection of claims 1, 2, 5 and 16-18 as obvious under 35 U.S.C. §103(a) over the PET-Radiopharmaceutical Dispensing Unit Manual, Nuclear Interface GmbH ("the Manual"), including the Supplement FDG Synthesizers ("the

Supplement"), in view of Damhaut et al. (U.S. Patent No. 6,172,207), and further in view of Asai et al. (U.S. Patent No. 5,536,491) and Stone-Elander et al. (U.S. Patent No. 5,308,944).

A. Status of the Manual and Supplement as Prior Art

In response to Applicant's arguments regarding the prior art status of the Manual and Supplement as prior art, the Office asserts that the Manual is "indeed a manual for operating instructions," and thus it is "obvious that the manual would be distributed to those who purchased/obtained such an instrument." Applicants respectfully disagree.

It is noted that, in support of its position, the Office states (on page 5, paragraph 15, of the present Office action) that "a reference is a 'printed publication' if it is accessible to the public and Examiner [sic] need not prove anyone actually looked at the document." To be clear - Applicants do not contend that **if** the manual was actually disseminated it would not qualify as prior art unless someone actually looked at it. Rather, Applicants contend that there is **no evidence of record** to support a conclusion that a sufficient showing has been made that the manual was **actually disseminated**. (See, e.g., *In re Wyer*, 655 F.2d 221, 227, 210 USPQ 790, 795 (CCPA 1981), which states "[a] reference is proven to be a 'printed publication' upon a satisfactory showing that such document **has been** disseminated or otherwise made available . . ." This case is cited in MPEP §2128, and further states that "the one who wishes to characterize the information, in whatever form it may be, as a 'printed publication' . . . should produce sufficient proof of its dissemination or that it has otherwise been available and accessible to persons concerned with the art.")

Accordingly, the Office's opinion that "it is obvious that the manual **would be** distributed" is not relevant to the issue at hand. Rather, the Office bears the burden of establishing that the manual was **actually disseminated**, and it has simply not done that here. More specifically, the submission of the document by a third party during prosecution of the corresponding European application, **without any details or supporting documentation** relating to its origin (e.g., details relating to how and when the document was actually disseminated), simply does not equate to a finding the document was actually disseminated. For instance, numerous situations are conceivable that explain the existence of the document, but that do not support the conclusion that the document was actually disseminated, including for example:

- The document is a revision (the document states "Last Revision: 10.12.2001" on its cover) of the manual and Nuclear Interface GmbH internally decided not to

provide the manual to customers because, for instance, (i) the design of the dispensing unit was changed before the document was disseminated, or (ii) the manual had incorrect information;

- The document is a revision of the manual, and sales of the dispensing unit were discontinued before it was disseminated;
- The document is an internal draft of the manual, or a draft of a revision to the manual, that was not disseminated before being further revised; and/or,
- The document was fabricated by the third party who submitted it the EPO and was never produced by Nuclear Interface GmbH.

The Office has failed to establish that any of the above scenarios did not occur and that the document was actually disseminated (to customers of Nuclear Interface GmbH or otherwise).

The Applicants draw the Examiner's attention to the prosecution of the corresponding European application (European Patent No. 1496946), wherein the European Examiner stated in the EPO's July 18, 2008 Office action (attached hereto):

> "A1 [Manual for PET – Radiopharmaceutical Dispensing Unit (Revision dated 10.12.2001); Nuclear Interface GmbH] and A2 [FDG Synthesizers, Supplement to the Manual and Operating Instructions (Revision dated 21.11.2001); Nuclear Interface GmbH] cannot be considered as having been made available to the public. In particular, the circumstances of the alleged distribution (prior use) have not been sufficiently substantiated. Therefore, the examining division does not intend to further investigate the matter."

While not precedential in the present application, when the European Patent Office was reviewing the manual reference and its supplement, it determined that the references could not "be considered as having been made available to the public" and were not thereafter considered as prior art in the prosecution of the European application, which has since been granted.

Further, even assuming *arguendo* that the document was disseminated, the Office has not established that dissemination of the document was not subject to a **confidentiality agreement**. (See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 908 F.2d 931, 15 USPQ2d 1321 (Fed. Cir. 1990), cited at MPEP §2128.01. That this case, four reports on the AESOP-B military computer system, which were not under security classification, were distributed to about fifty organizations involved in the AESOP-B project. One document contained the legend

"Reproduction or further dissemination is not authorized." The other documents were of the class that would contain this legend. The documents were housed in Mitre Corporation's library. Access to this library was restricted to those involved in the AESOP-B project. The court held that public access was insufficient to make the documents "printed publications.")

In addition to failing to establish that the document was in fact disseminated, or that it was not disseminated subject to a confidentiality agreement, the Office has failed to establish that the document was disseminated prior to the effective filing date of the present application. More specifically, it is to be noted that the present application claims priority to a PCT patent application filed on April 23, 2003, which in turn claims priority to a European patent application filed April 24, 2002. The Manual lists October 12, 2001 as its "Last Revision" date. However, the Office has not established that the document was actually disseminated by a date effective to establish the document as a valid prior art reference under 35 U.S.C. §102. (See, e.g., *Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986), cited at MPEP §2128, wherein the court held that since there was no proof regarding whether a mailer was received by the public prior to the filing date of the application at issue, there could be no rejection under 35 U.S.C. §102(a). See also MPEP §2128, which states in reference to internet and on-line databases that "if the publication itself does not include a publication date (or retrieval date), it cannot be relied upon as prior art under 35 U.S.C. 102(a) or (b).") The Applicants respectfully submit that the mere identification of the revision dates on the face of the references do not determine or shed light on the actual publication dates of the references. Therefore, without the Office providing proof of actual dissemination of the references to the public, the references cannot be cited as prior art against the present application.

In view of the foregoing, Applicants respectfully submit that the Office has not met its burden here to establish that the cited document is prior art. Applicants therefore request that the Office withdraw all rejections based thereon, or provide additional evidence to establish that the document was disseminated.

B. The Claimed Subject Matter

Claim 1 is directed to a method for improving radiostability of a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution during autoclaving. The method of claim 1 as amended comprises the steps of: (a) providing a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution; (b) adding at least one buffer based on a weak acid consisting of citrate, acetate, ascorbate and combinations thereof to the ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution; and (c) autoclaving the buffered ^{18}F-fluor-deoxy-

glucose (^{18}F-FDG)-solution. As indicated in the specification (see, e.g., paragraphs [0003-0004] of the published application, U.S. Publication No. 2005/017553), Applicants have discovered a method for preparing a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution that is sufficiently sterile and stable for use (i.e., for injection in a patient in need thereof). Sterilization is achieved by autoclaving a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution that has been sufficiently buffered with a solution of a weak acid. In this way, a sterilized solution is obtained that still meets the specification of more than 95% radiochemical purity eight hours after production.

In view of Applicants' position that the Manual and Supplement are not prior art against the present application, Applicants will direct the remainder of their comments on the present rejection toward the combination of Damhaut et al., Asai et al. and Stone-Elander et al. only. In the interest of brevity, Applicants will not again characterize Damhaut et al., Asai et al. and Stone-Elander et al., but rather incorporate by reference the characterizations in their January 5, 2009 letter to the Office (entitled "Amendment C After Final Rejection and Request For Continued Examination").

C. Independent Claim 1 and Claims Depending Therefrom are not Obvious

The Office appears to base the present rejection on (1) the substitution of the citrate buffer of Damhaut et al. for the analogous buffer disclosed in the Manual for improving the stability of a FDG solution (item 10 on page 4 of the Office action), and (2) the substitution of the autoclaving sterilization method of Asai et al. for the sterilization method of Damhaut et al. (item 11 of page 4 of the Office action). Applicants will address only the second basis of the present rejection below, as this one does not fully rely on the use of the Manual as a prior art reference.

With respect to the Office's combination of Asai et al. with Damhaut et al., the Office seems to base its obviousness rationale here on a simple substitution of one known element (autoclaving process of Asai et al.) for another (use of filtration to purify and sterilize) to obtain predictable results. Under this rationale, to establish a *prima facie* case of obviousness, the Office must establish that: (1) the prior art contained a method which differed from the claimed method by the substitution of one or more steps therein; (2) the substituted steps and their functions were known in the art; (3) one of ordinary skill in the art could have substituted one known step for another, and the results of the substitution would have been predictable; and, (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. (See, e.g., MPEP §2143.) Applicants submit that the Office has, at a minimum, failed to show that the prior

art contained a method which differed from the claimed method by the substitution of one or more steps therein, and/or that the one of ordinary skill in the art would have known to substitute one known step for another, and/or that the results of the substitution would have been predictable.

Damhaut et al. teach preparation of ^{18}F-FDG that is purified and sterilized. Notably, however, they indicate that the pH of the final solution may be adjusted by **adding a** citrate or sodium phosphate **buffer after purification and sterilization**. Accordingly, if the autoclaving step of Asai et al. were substituted for the filtration step of Damhaut et al. in order to achieve purification and sterilization, the buffer would be added **after** autoclaving of the solution. As a result, radiostability of ^{18}F-FDG would not be improved. Alternatively, one of ordinary skill in the art would have to find some motivation to **rearrange** the steps of Damhaut et al., in addition to substituting the autoclaving step of Asai et al. for the filtration step of Damhuat et al. Applicants submit there is no such motivation.

Applicants further submit that the Office has also failed to establish the results of the substitution of the autoclaving step of Asai et al. for the filtering step of Damhaut et al. would be predictable. Specifically, even assuming *arguendo* that one of ordinary skill in the art would some how find motivation to rearrange the process steps of Damhaut et al., such that the buffer were added prior to autoclaving, the Office has not set forth why one of ordinary skill in the art would expect the buffer to provide radiostability-enhancing properties. The Office has not established that this result would be predictable, and there is no other reasoning or articulation on record regarding motivation to rearrange the processing steps of Damhaut et al.

Finally, Applicants submit that one of ordinary skill in the art would in fact **not** combine the autoclaving step of Asai et al. with the ^{18}F-FDG preparation method of Damhaut et al. This is because Damhaut et al. actually ***teach away*** from use of an autoclaving step, in that they disparage the use of process steps that require heating. Specifically, according to the abstract, the process of Damhaut et al. "is more rapid than conventional methods and is **performed at room temperature** rather than high temperature for conventional technology." According to Damhaut et al., such heating steps are undesirable, as they add to the total preparation time (see col. 2, lines 9-15; col. 5, lines 66-67). In view of this disclosure, Applicants submit that one of ordinary skill in the art would not have combined the references regardless of any high-temperature stability of the ^{18}F-isotope or FGD compound set forth in the Stone-Elander et al. reference or in the Manual. (It is improper to combine references where the references teach away from their combination, per MPEP §2145.)

In view of the foregoing, the Office has clearly failed to establish a *prima facie* case of obviousness. Applicants therefore submit that the subject matter of claim 1, as well as all claims depending therefrom, is patentable over the cited references, both alone and in combination. Withdrawal of the present rejection is therefore requested.

Conclusion

In view of the foregoing, Applicants request favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account No. 13-1160 for any fees that may be required for this Amendment D in the name of Mallinckrodt Inc.

Respectfully Submitted,

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Dse 25/09/08

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Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 2 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

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Loher, Florian
Primary Examiner
For the Examining Division

Enclosure(s): 1 page/s reasons (Form 2906)

The examination is being carried out on the **following application documents:**

Description, Pages

1-8 as published

Claims, Numbers

1-16 received on 12.03.2008 with letter of 11.03.2008

A1 and A2 cannot be considered as having been made available to the public. In particular, the circumstances of the alleged distribution (prior use) have not been sufficiently substantiated.Therefore, the examining division does not intend to further investigate the matter.

The subject-matter of present claims 1-16 fulfills the criteria of the EPC.

The applicant is asked to adapt the description to the subject-matter for which protection is sought in the present set of claims. The applicant should take care that the wording in the description is in accordance with Articles 53(c) EPC, Rule 48(1)(c) EPC, the Guidelines C-II 4.19 and the Guidelines C-III-4.12

In addition, the relevant prior art documents have to be cited and should be discussed briefly in the description (Rule 42(1)(b) EPC).